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Evans Syndrome: A Case Report and Review

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Abstract

Evans Syndrome (ES) is defined as the concomitant or sequential association of warm Autoimmune Hemolytic Anemia (AIHA) with Immune Thrombocytopenic Purpura (ITP), and less frequently autoimmune neutropenia. Its chronic course is characterized by recurrent relapses and remissions. The typical clinical course is chronic and relapsing, and therapy is generally progressive and of poor outcome. We present a case of evans syndrome who was doing well on treatment with azathioprine and steroids but deteriorated and succumbed to her illness due to non compliance.

Introduction

Evans Syndrome (ES) is defined as the concomitant or sequential association of warm Autoimmune Hemolytic Anemia (AIHA) with Immune Thrombocytopenic Purpura (ITP), and less frequently autoimmune neutropenia [1,2]. In this rare disorder body makes antibodies against one's self Red Blood Cells (RBCs), White Blood Cells (WBCs) and Platelets. Individuals may manifest signs and symptoms due to anemia, low platelets and leukocytes. When AIHA and ITP occur concomitantly, the diagnosis must exclude differentials such as thrombotic microangiopathies, anemia due to bleeding complicating ITP, vitamin deficiencies, myelodysplastic syndromes, paroxysmal nocturnal hemoglobinuria, or specific conditions like Hemolysis, Elevated Liver Enzymes and Low Platelets (HELLP) when occurring during pregnancy [2].

ES does not show variation by age, gender or ethnic groups. Its chronic course is characterized by recurrent relapses and remissions. First-line therapy includes corticosteroids and intravenous immunoglobulin with good clinical response, although relapse is frequent. Immunosuppressive drugs and splenectomy may be considered when first line treatment has failed [2,3]. Long-term survival data are limited. In patients followed for a median range of 3-8 years, mortality ranged from 7-36% [4]. The main causes of death were hemorrhage and sepsis. In this case review, we discuss a 25-year-old female with a long-standing history of ES who developed ulcer on dorsum of right foot, fever, dyspnoea, generalized weakness and menorrhagia. We are interested in reporting this case because the clinical presentation of patient with such scenarios will compel the treating physician to look for Evans Syndrome and properly diagnose it.

Case Presentation

A 25 years old married female came to our hospital with complaints of an ulcer of 5x6cm size over dorsum of right foot with persistent fever, nausea, vomiting, dyspnoea on exertion and generalised weakness since last 7-10 days. There were no complaints of headache, cough, abdominal pain, trauma or black stools.

There was history of admission at another hospital for miscarriage two years earlier. After ten days she developed bleed-

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ing from gums and teeth due to severe thrombocytopenia and needed multiple platelets and packed cell transfusions. They took discharge from the hospital but after that she had menstrual bleeding continuously for one month and accompanied with weakness. Following which she went to another hospital after two months of previous discharge with complaints of weakness and bleeding for which she was again given platelets and packed cell transfusions (PCV) and was referred to higher centre for further investigations and management in view of recurring complaints. Hence, she was brought to Parul Sevashram Hospital on 19/04/2022 where after investigations (Table 1) she was diagnosed as Evans Syndrome and intravenous steroids and azathioprine were started. She gradually improved and was discharged in stable condition on oral steroids and azathioprine. On follow up she showed good response to steroids. Later in the course, slowly steroids were tapered off and oral mycophenolate mofetil was started but her blood counts deteriorated and she was again admitted and PCV transfusion was given. In view of these events steroids were started again. Since then she was doing well till ten days ago when she walked barefoot for 7-8 kilometres as part of a religious ritual and developed blisters on foot following which she stopped all medicines and later presented at our hospital with the complaints as described. There was no history of diabetes, hypertension, tuberculosis, asthma or any other medical illness or surgery.

On examination, the patient had pallor but icterus, cyanosis, clubbing, oedema or lymphadenopathy were not seen. She had PR-98/min, BP-112/76 mm/Hg and spO2- 98% on room air. Systemic examination was unremarkable. An ulcer of size 5x6 cm having serous discharge and reddish black base was noted over dorsum of right foot. It was painful but didn't bleed on touch. Steroids and azathioprine were started again and daily dressing was done after blister drainage. Antibiotics were started which were then altered according to pus culture and sensitivity reports. After one week of treatment she recovered and was discharged with advise to comply with the advised medicines and daily dressing.

However, the patient was non compliant and didn't do any dressings at home. After around ten days, patient had to be admitted again with complaints of fever with chills, nausea, multiple episodes of vomiting and severe weakness. Her hemoglobin was low and again PCV were transfused and symptomatic and supportive treatment was started with antibiotics. However, this time she didn't respond to the treatment and after a few days, developed altered sensorium, unequal pupils poorly reacting to light. An urgent CT head was done which showed large intracranial haemorrhage. She was put on ventilatory support in view of very poor general condition and diminished spontaneous respiratory efforts. Her condition deteriorated, she developed sepsis with septic shock and succumbed to her illness on the next day.

Table 1: Lab reports.

	Normal Range	19/04	21/04	25/04	24/05	15/2	01/03
Hb(g/dL)	13-17	4.5	5.8	6.3	8.7	10.3	3.1
RBCs(10^{12}/L)	4.5-5.5	-	-	-	3.37	-	0.23
Platelets(/Micro Litre)	1.5-4.5 x10^5	2000	5000	20000	62000	7000	15000
Total count(/cmm)	4000-7000	4050	7110	8750	8500	7370	10930
Lymphocytes(%)	20-40	46	23	36	24	-	30
Neutrophils(%)	50-62	-	-	-	73	-	61
Eosinophils(%)	0-6	1	1	1	01	-	01
Monocytes(%)	0-10	6	2	6	02	-	01
S. creatinine(mg/dl)	0.6-1.1	0.80				0.6	-
SGPT(U/L)	Upto 45	19	16	19	16		16
APTT(seconds)		30.50	-	-	-		-
PCV(%)		-	-	-	26.3		4.0
MCV(fl)		-	-	-	81.9		70
MCH(pg)		-	-	-	25.8		132.4
MCHC(g/dL)		-	-	-	30.5		77.9
K+(mmol/L)		-	-	-	-	4.0	3.6
Na+(mmol/L)		-	-	-	-	141	131
Cl(mmol/L)		-	-	-	-	108	95
CT-Scan(Brain)	Large intracranial hemorrhage						
ECG	Normal						
USG Abdomen							
Chest-Xray							
Bone marrow	Normal						
LFT	Normal						
Urine RM and Hb	Normal, No hemoglobinuria						
Vitamin B12	>2000						
DAT	Positive						

Review and Discussion

Robert Evans first described Evans syndrome in 1951. Its etiology is not known but the pathogenesis is said to be based on immune dysregulation. It has been suggested that autoreactive, antibody-producing B cells are activated due to constitutive IL-10 and INF production [5], as seen in other autoimmune disorders, leading to cytopenia. Second cytopenia may appear months to years after the first immune cytopenia which may be the reason for delay in diagnosis. Neutropenia occurs in up to 55% of patients at presentation. Clinical presentation may be accounted for by symptoms of hemolysis (lethargy, fever, pallor and yellowish sclera) and thrombocytopenia (petechiae, bruising and mucocutaneous bleeding). Lymphadenopathy, hepatomegaly and/or splenomegaly may also be present. These signs may be seen in same case during acute exacerbations and may be chronic or intermittent.

The diagnosis needs a high index of suspicion with exclusion of other disorders characterized by AIHA and ITP [3,6,7]. Presence of cytopenia in complete blood count and a blood film showing features of AIHA (polychromasia, spherocytes) with absence of features of other underlying diagnosis (malignancies, micro angiopathic haemolytic anaemia, congenital haemolytic and thrombocytopenic conditions) raise suspicion. A positive direct Coombs test suggests the diagnosis of haemolytic anaemia, although it may be positive even in the absence of haemolytic anaemia. Other features of haemolysis including a raised reticulocyte count, unconjugated hyperbilirubinaemia and decreased haptoglobins should also be looked for. The Direct Antiglobulin Test (DAT) is almost invariably positive (although often weakly so), even in the absence of haemolytic anaemia, and may be positive for IgG and/or complement (C3) [4, 8-10]. The indirect antiglobulin test may also be positive in 52-83% of patients [11]. Assays for antiplatelet and antigranulocyte antibodies have shown varied results [12]. Other causes of acquired immune cytopenia like Systemic Lupus Erythematosus (SLE), IgA deficiency, Common Variable Immunodeficiency (CVID), Human Immunodeficiency Virus (HIV), Autoimmune Lymphoproliferative Syndrome (ALPS), TTP, Hemolytic Uremic Syndrome (HUS) should be excluded [13,14]. Bone marrow examination is necessary to diagnose ES and exclude infiltrative process in patients with pancytopenia, especially before starting steroid therapy.

First-line therapy for ES is corticosteroids and/or intravenous immunoglobulin, blood and/or platelet transfusions in severe cases according to requirement. Immunosuppressive agents such as cyclosporin, mycophenolate mofetil, vincristine and danazol may be considered as second line therapy individualized, based on patient's age, natural history and severity of the disease. Rituximab (monoclonal anti-CD20 antibody) may be used in case of resistance to both first- and second-line therapies. Third-line therapy includes oral cyclophosphamide (1-2 mg/Kg/die for 2-3 months) or intravenous monoclonal anti-CD52 antibodies. Autologous and allogenic stem cell transplantation may be sought in a limited number of patients, after failure of pharmacological treatment.

Our patient was diagnosed in time and was doing fine on treatment, but deteriorated and succumbed due to noncompliance. Similar case was reported from one of the tertiary care centers in Nepal where a thirty-two years old female presented with intracranial hemorrhage, she was kept on a high dose of intravenous mannitol, platelet-rich plasma, steroids and immunomodulator azathioprine but unfortunately, she also died due to noncompliance with therapy [4].

We presented this case to emphasize on the importance of compliance to treatment as any negligence to compliance may lead to disastrous and ominous result where progression can be controlled with treatment leading to near normal quality of life.

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